METAL CATION MEDIATED HYDROLYSIS OF PHOSPHONO-FORMATE DIESTERS: CHEMOSELECTIVITY AND CATALYSIS

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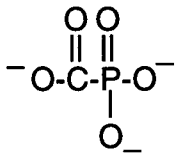
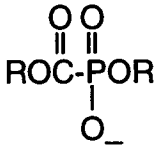
PHOSPHONOFORMATES



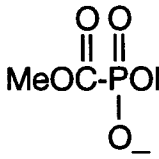
Phosphonoformate trianion ("Foscarnet") is an antiviral agent active against herpes simplex and AIDS-related cytomegalovirus.

Poor membrane permeability. Phosphonoformate diesters and triesters of interest as "prodrugs."

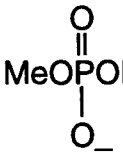
Monoanionic phosphonoformate *diesters* exhibit antiviral activity in prodrug studies.



DIMETHYLPHOSPHONOFORMATE



(DMPF) is the parent phosphonoformate diester.

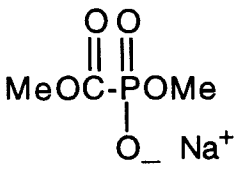


(DMP) resembles DMPF.

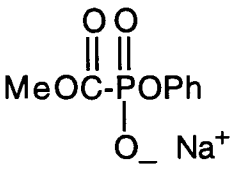
How will metal cation cleavage of DMPF compare to that of DMP?

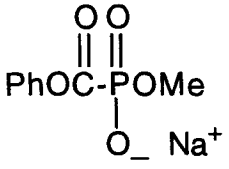
DMPF has 3 sites for cleavage: O-C, P-O, and C-P. What sort of *chemoselectivity* can be observed?

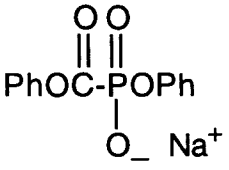
SUBSTRATES AND METAL CATIONS



(DMPF)



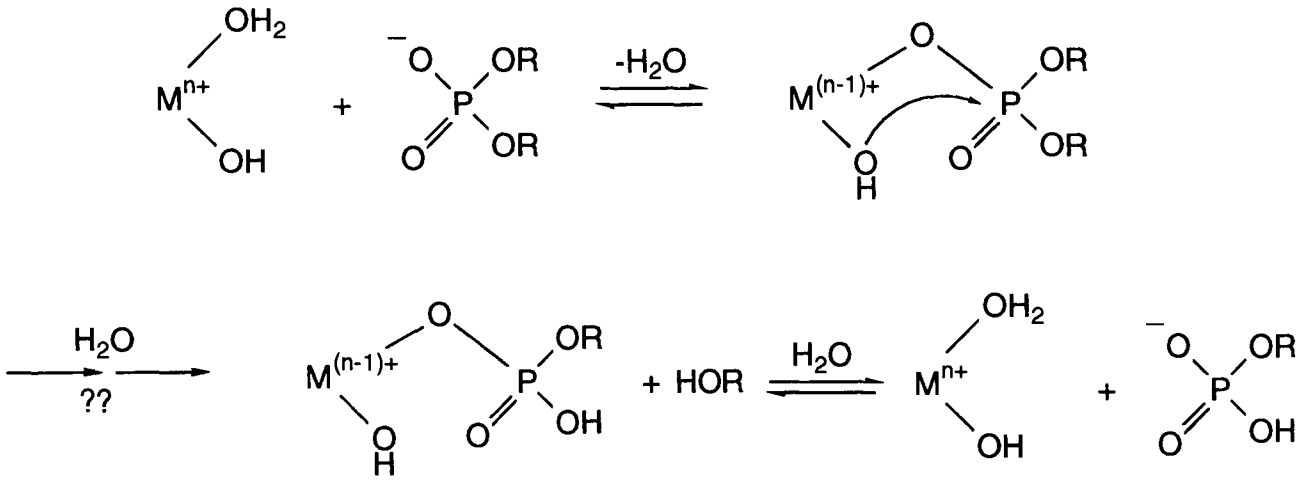




Ce^{4+} Th^{4+} Zr^{4+} Hf^{4+}

Why these cations?

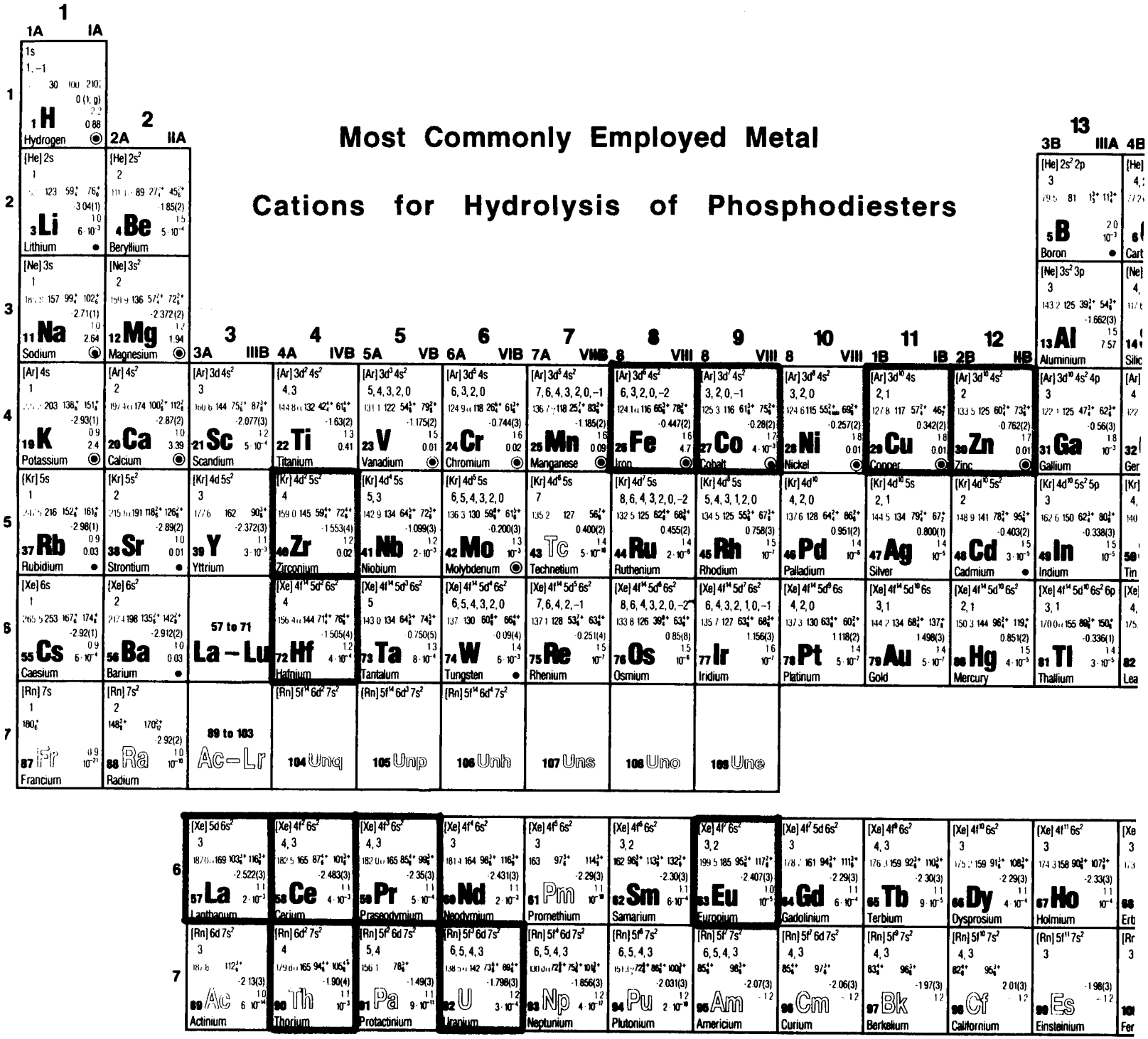
POLYVALENT METAL CATIONS CAN MEDIATE PHOSPHODIESTER HYDROLYSIS



M^{n+} provides electrophilic/nucleophilic catalysis. Require good Lewis acidity to bind P-O^- and to acidify H_2O of hydration to afford metal bound OH nucleophile. Turnover catalysis is possible in some cases.

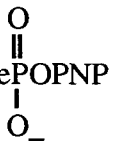
Desire highly charged, small M^{n+} ("hard" cation"), but also with high-lying vacant d or f orbitals to bind P-O^-, *transition metals, lanthanides, or actinides.*

Most Commonly Employed Metal Cations for Hydrolysis of Phosphodiesters



METAL ION CATALYZED CLEAVAGES OF

PHOSPHONATE MONOESTERS

Substrate PNPMP: 

H_2O, pH 7.6, 30 °C, $k_{hydrol} = 2.0 \times 10^{-9}\ s^{-1}$; $k_2 = 3.6 \times 10^{-11}\ M^{-1}s^{-1}$

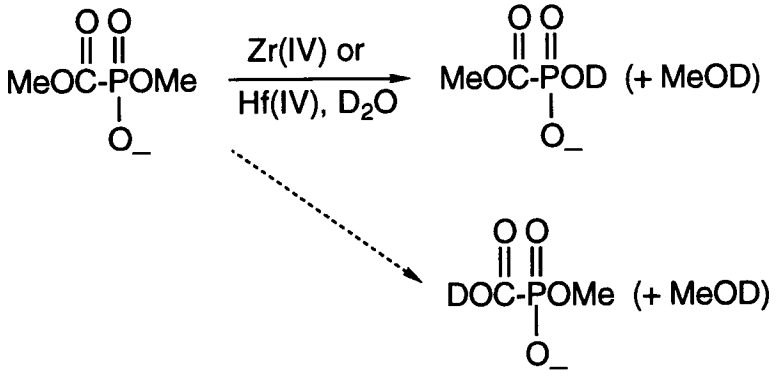
M^{4+}	pH	Brij, mM	k_{obs}, s^{-1}	k_{obs}/k_o
Zr^{4+}	3.5	0.0	0.11	5.5×10^7
Ce^{4+}	4.0	2.0	0.036	1.8×10^7
Th^{4+}	6.0	2.0	0.015	7.5×10^6

With 0.05 mM PNPMP, 1.0 mM M^{4+}, 37 °C.

Note enormous accelerations with Zr^{4+}, Ce^{4+}, and Th^{4+}. *Polymer or resin-bound M^{4+} might be excellent materials for the degradation of phosphonate monoesters.*

In the Zr^{4+} case, the half-life of PNPMP is reduced from 11 years to 6.3 seconds!

Zr(IV) or Hf(IV) CLEAVAGE OF DMPF

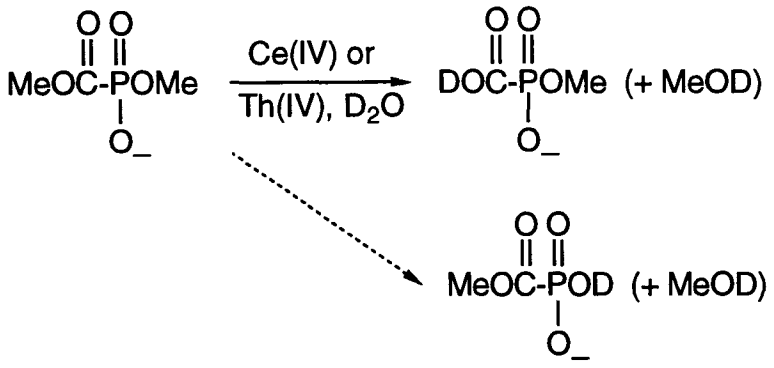


Kinetics are followed by monitoring released MeOD (^{1}H NMR); products are monitored by ^{31}P NMR.

M(IV)	$10^4 k_{obs}$ (s^{-1})	% P-OMe	% C-OMe	$k_{M(IV)}/k_{D+}$
Zr	4.4	79	21	3300
Hf	4.0	90	10	3100

Zr and Hf exhibit *P-O chemoselectivity*, with significant hydrolytic acceleration.

Ce(IV) or Th(IV) CLEAVAGE OF DMPF



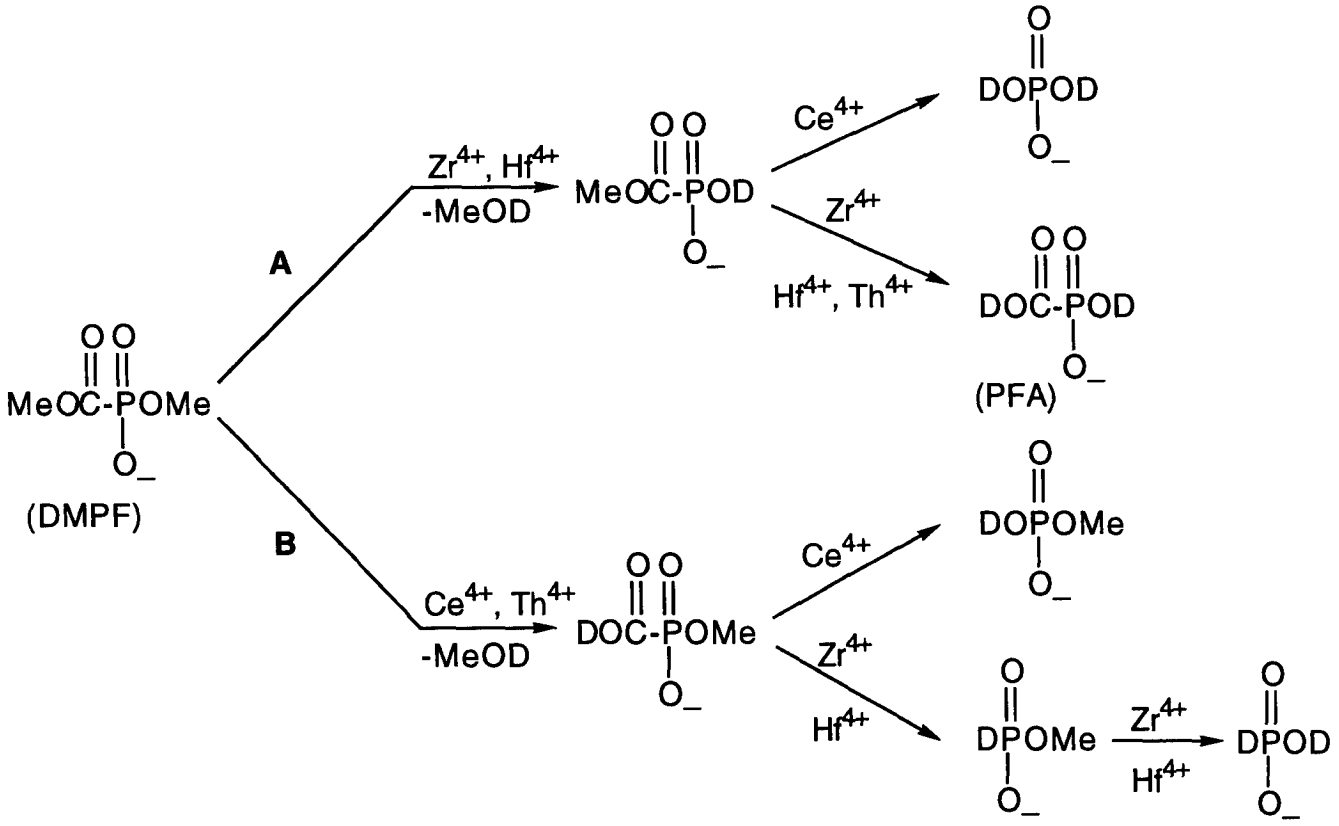
Kinetics are followed by monitoring released MeOD (^{1}H NMR); products are monitored by ^{31}P NMR.

M(IV)	$10^4 k_{obs}$ (s^{-1})	% P-OMe	% C-OMe	$k_{M(IV)}/k_{D+}$
Th	1.3	--	95	980
Ce	5.2	10	90	3900

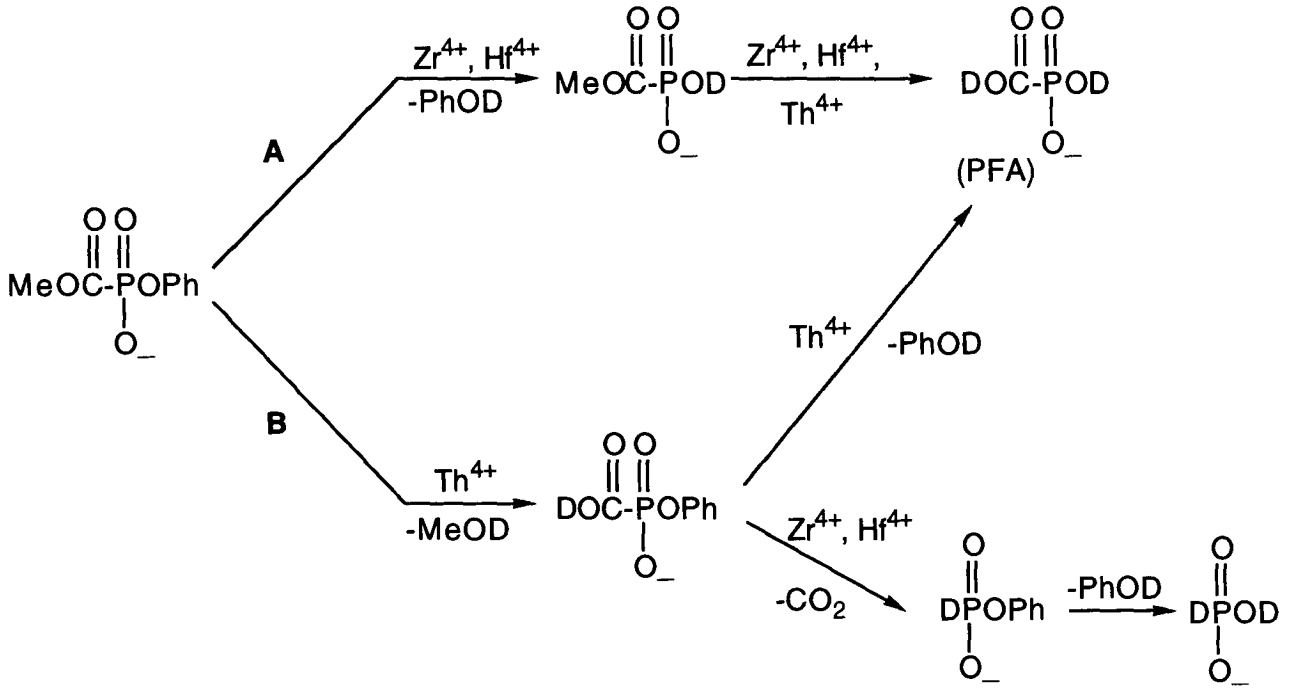
Th and Ce exhibit *C-O chemoselectivity*, with significant hydrolytic acceleration.

OVERVIEW OF DMPF REACTIONS

Cleavages of the monoesters are 10-100 times slower than cleavages of DMPF



CLEAVAGE OF C-OMe/P-OPh PHOSPHONOFORMATE



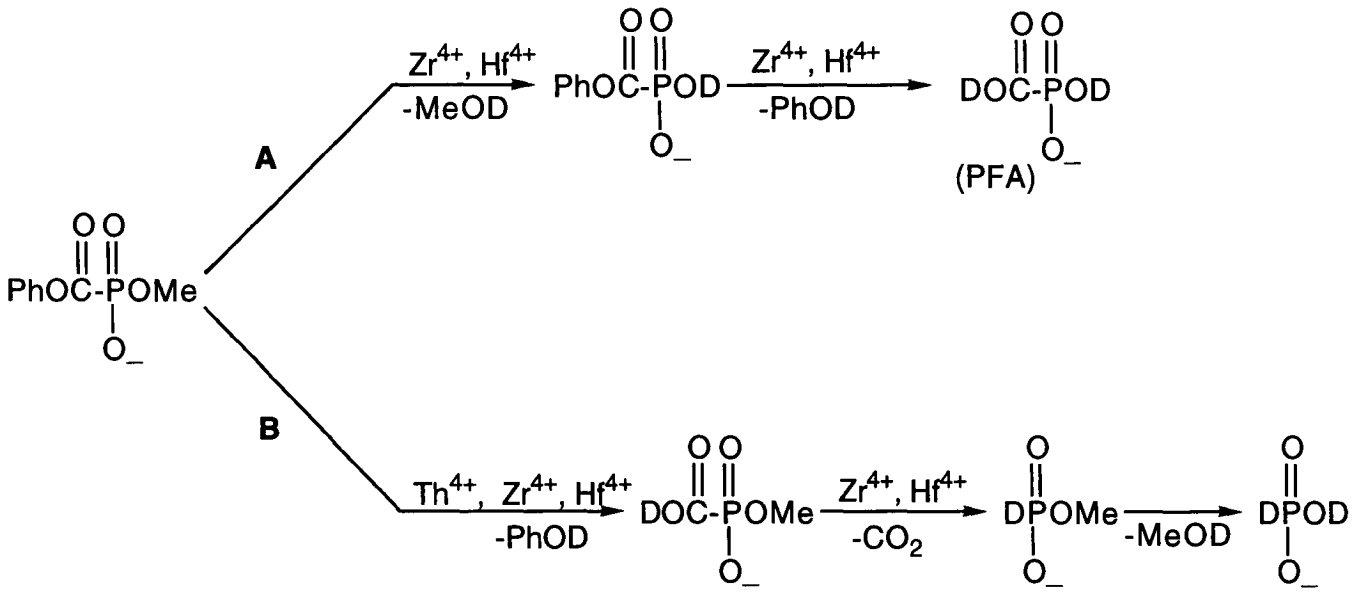
1. For Pathway A at pD 1.7 or 2.2:
$k_{Zr} = 2.3 \times 10^{-2}\ s^{-1}$; $k_{Hf} = 0.65 \times 10^{-2}\ s^{-1}$. Faster than DMPF cleavage.

Selectivity for Zr^{4+} and Hf^{4+} is >95% P-OPh cleavage.

2. For Pathway B, Th^{4+} is >95% selective for C-OMe cleavage;
$k_{Th} = 1.6 \times 10^{-4}\ s^{-1}$.

3. Chemoselectivity seen with DMPF is preserved.

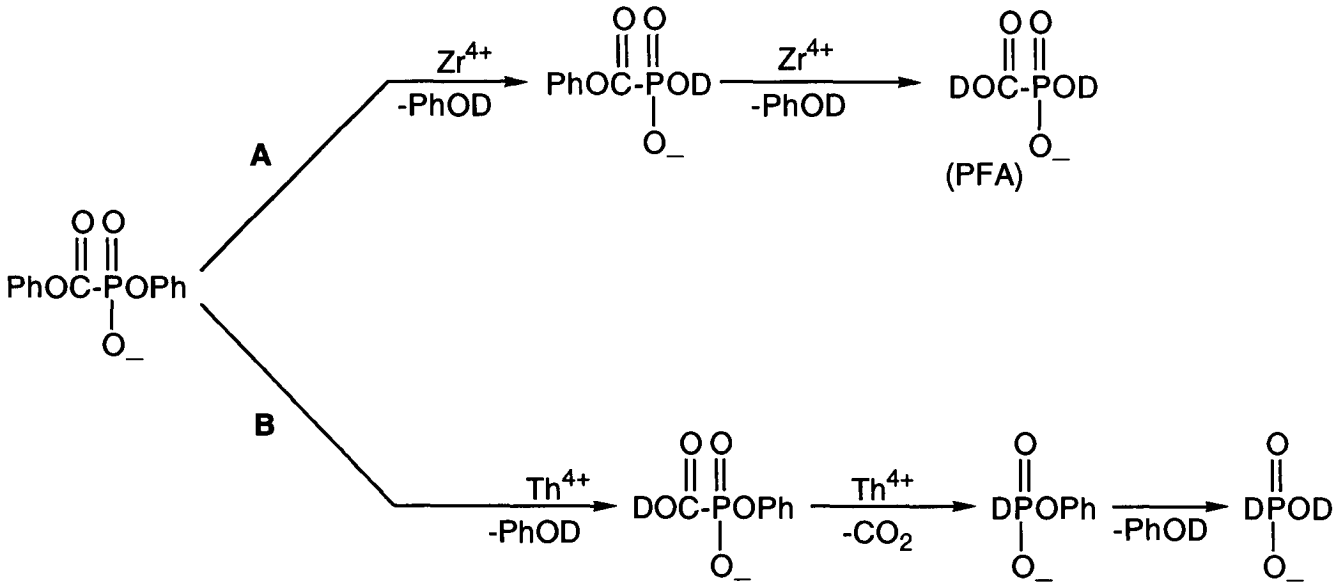
CLEAVAGE OF C-OPh/P-OMe PHOSPHONOFORMATE



With the better PhO leaving group now at C, the P-chemoselectivity of Zr^{4+} or Th^{4+} is lost. Here, C-OPh cleavage > P-OMe cleavage by 90:10 (Zr) or 79:21 (Hf): $k_{Zr} = 1.79 \times 10^{-2}\ s^{-1}$, $k_{Hf} = 0.61 \times 10^{-2}\ s^{-1}$.

Th^{4+} gives >95% C-OPh cleavage, as expected: $k_{Th} = 0.18 \times 10^{-2}\ s^{-1}$.

CLEAVAGE OF C-OPh/P-OPh PHOSPHONOFORMATE



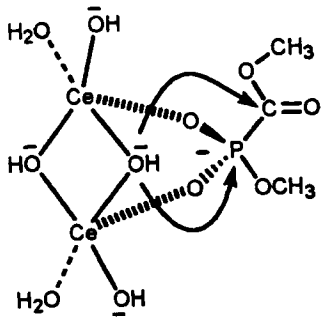
1. Cleavage by Zr^{4+} was >95% P-selective; $k_{Zr} = 1.3 \times 10^{-2}\ s^{-1}$ in 1:1 D_2O/CD_3CN at pD 1.7.

2. Cleavage by Th^{4+} was 90:10 C-selective: $k_{Th} = 4.7 \times 10^{-3}\ s^{-1}$ at pD 3.1 in D_2O/CD_3CN.

3. Chemoselectivity here is analogous to DMPF.

SOURCE OF CHEMOSELECTIVITY

At pH 2-3, Ce(IV) and Th(IV) will be mainly dimeric or monomeric.



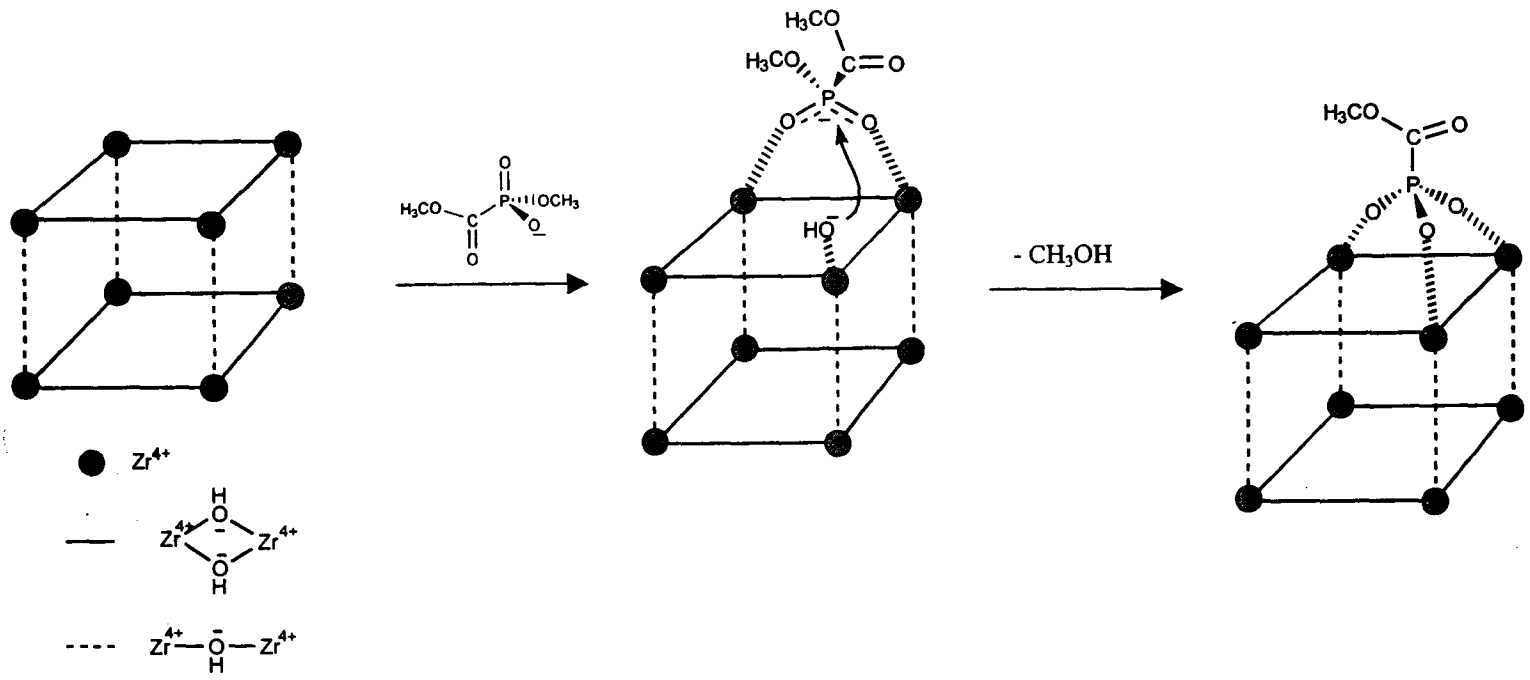
OH^- attack at C=O involves a 5-membered cyclic TS; OH^- attack at P-OMe involves a 4-membered cyclic TS.

Attack at *trigonal* C in 5-membered cyclic TS (addition-elimination) is kinetically preferred to attack at *tetrahedral* P (S_N2) in 4-membered cyclic TS.

Ce(IV) and Th(IV) afford C-O chemoselectivity.

P-O CHEMOSELECTIVITY

At pH ~ 2, Zr(IV), and presumably Hf(IV), exist as octamers or tetramers:



Cleavage at P can now occur via a 6-membered cyclic TS and lead directly to a tripodal phosphonate product with the same structure as the lamellar Zr phosphonates. Zr(IV) and Hf(IV) give P-O chemoselectivity.

P-O CHEMOSELECTIVITY LINKED TO M(IV) OCTAMERS

	P-O		C-O	
	Zr	Hf	Zr	Hf
M(IV)	79	90	21	10
M(IV) + Tris (1:1)[a]	40	66	60	34
M(IV) + Tris(1:2)[a]	15	19	85	81
M(IV) + NaOD (1:1)[b]	50	58	50	42

[a]Tris forms 1:1 complexes with Zr(IV). [b] OH^- promotes formation of Zr oligomers.

Destruction of M(IV) octamers/tetramers shifts P-O to C-O chemoselectivity.

SUMMARY

1. Ce^{4+}, Th^{4+}, Zr^{4+}, and Hf^{4+} ions accelerate the hydrolysis of phosphono-formate diesters.

2. With identical C-OR and P-OR leaving groups, Zr^{4+} and Hf^{4+} direct scission to the P-O ester site, whereas Ce^{4+} and Th^{4+} mediate attack at the C-O site.

3. Leaving group efficiency (PhO > MeO) can modulate the chemoselectivity.

4. P-O selectivity is associated with tetrameric or octameric forms of Zr^{4+} or Hf^{4+} aqueous complexes.

5. C-O selectivity is associated with dinuclear or mononuclear forms of Ce^{4+} or Th^{4+}.